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Food and Drug Administration
Department of Health and Human Services
5630 Fishers Lane, Room 1061
Rockville, Maryland 20652

Citizen's Petition

The undersigned, on behalf of Watson Pharma, Inc. ("Watson"), a subsidiary of Watson Pharmaceuticals, Inc., submits this petition under Sections 505(b) and 505(j) of the Federal Food, Drug, and Cosmetic Act (FDCA) (21 U.S.C. §§ 355 (b) and (j)) and 21 C.F.R. § 10.30, to request that the Commissioner of Food and Drugs withhold approval of any Abbreviated New Drug Application (ANDA) for a generic version of Ferrlecit® (sodium ferric gluconate complex in sucrose) until the conditions set forth in this petition are satisfied.

A. Actions Requested

Watson asks that FDA not approve any ANDA citing Ferrlecit® as the reference listed drug (RLD) unless the:

1. process used to manufacture the generic product has been adequately demonstrated to be the same as Watson's manufacturing process for Ferrlecit®, and

2. physiocochemical characteristics of the generic product are the same as those of Ferrlecit® , and

3. the active ingredient or, in this case, the final generic product can be adequately demonstrated to be the "same as" that of the reference listed drug

If all of the above requirement cannot be met then the FDA should require that the applicant submit an NDA supported by a demonstration of equivalent safety and effectiveness based on results of appropriate preclinical and clinical studies.

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B. Statement of Grounds

1. Introduction and Background

The Food Drug and Cosmetic Act requires that any person filing an Abbreviated New Drug Application for a drug containing a single active ingredient must demonstrate that the active ingredient of the new drug is the same as that of the approved reference drug.[1] As discussed in detail below, a manufacturer of generic sodium ferric gluconate complex in sucrose for injection will not be able to produce the same active ingredient or final product as Ferrlecit® unless they use the exact manufacturing process used by Watson. If the exact process is not used, the FDA must require that the sponsor of the generic product demonstrate that the effectiveness and safety of their product is equivalent to that of Ferrlecit® by performing adequate preclinical and clinical studies.

Ferrlecit® is an iron supplement for intravenous administration. It is a high molecular weight macromolecule known as sodium ferric gluconate complex in sucrose. It differs both structurally and chemically from the other types of parenteral iron supplements on the market, i.e., iron dextran and iron sucrose. Because the process used to manufacture Ferrlecit® is complex and employs both specialized equipment and tightly controlled processes, the manufacturing process is critical to the final structure of the Ferrlecit® macromolecule. In addition, because of the complexity of the macromolecule, its structure has yet to be determined and can only be partially inferred from physicochemical testing. Therefore, until the exact structure of the Ferrlecit® macromolecule can be established, it is impossible to determine if two products, made by different manufacturers, are the same.

2. History of Injectable Iron Compounds

In the 1950s Fisons Pharmaceuticals introduced the first injectable iron product Imferon®, an iron dextran, in the United States. Iron dextrans are colloidal solutions of ferric hydroxide solubilized by partially hydrolyzed dextran of low molecular weight. FDA accepted this product in 1968 according to the provisions of a DESI-review.[2] In 1990, Fisons withdrew the product from the market due to manufacturing issues related to particulate matter. In 1992 Schein Pharmaceuticals introduced a new injectable iron dextran product called INFeD®. In 1995 American Regent introduced another iron dextran called Dexferrum®. These two iron dextrans are not exactly the same; the iron complexes in INFeD® have a significantly lower average molecular weight than those in Dexferrum®, but both are considered to be iron dextrans. None of the iron dextran products are rated as therapeutically equivalent to one another.

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[1] 21 U.S.C. § 355(j)(2)(A)(ii)(I)

[2] FDA Review of Pharmacokinetics and Iron Utilization Studies, November 28, 1995, ANDA 40-024, Iron Dextran Injection, USP, Luitpold Pharmaceuticals, Inc.

While iron dextran, iron sucrose and sodium ferric gluconate complex in sucrose are all considered parenteral iron supplements, they differ greatly in their molecular weights. Ferrlecit® is the largest molecular weight product of all the parenteral iron preparations, and therefore, the most chemically complex. As will be discussed later, molecular weight may have an impact on both the effectiveness of these products, as well as their safety profiles.

3. FDA should not approve any ANDA referencing Ferrlecit® unless the generic product has been shown to be manufactured according to the same process as Watson's, or the safety and effectiveness of the generic product has been shown to be equivalent to Ferrlecit® in adequate clinical studies.

a. The Manufacturing Process Of Product Is Extremely Complicated, Difficult To Reproduce And Creates The Distinct Chemical Structure Of Ferrlecit®.

The Ferrlecit® manufacturing process was developed almost 45 years ago and is unique in that it starts with simple components and proceeds through a series of carefully-controlled chemical reactions and purification/sterilization steps to produce the final macromolecular product. It is also unique in that there is no identifiable active ingredient before the creation of the final product: sodium ferric gluconate polymers in an aqueous sucrose solution. Because of these facts, the process must be strictly controlled with numerous in-process tests to assure the identity, strength, quality, purity and reproducibility of the final drug product.

The actual manufacturing process is a multi-step process involving numerous individual ingredients which must be combined in a specific order, at specific rates and under specific conditions for the reaction to proceed correctly. Even the configuration of the reaction vessel can be critical, because a controlled heterogeneous chemical reaction is a critical step in the preparation of Ferrlecit®. The process therefore uses custom designed equipment that was created specifically for the production of this product. Reaction temperatures, pH, filtration, and addition, stirring and flow rates must be controlled throughout the process to reproducibly create the Ferrlecit® drug product. Variations in any of these parameters throughout the manufacturing process could result in critical changes to the final product.[7]

The manufacturing process was originally developed in 1959 and subsequently transferred to a different manufacturing facility which still manufacturers the product. When the production was transferred to the current facility, the actual production equipment was also transferred in order to minimize any variation in the process. With only minor modifications to the filtration technology, this equipment is still being used today.[8]

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[7] Data on file at Watson Pharma.

[8] Data on file at Watson Pharma.

b. Physicochemical differences resulting from different methods of production could have a negative impact on the efficacy of a generic product.

In its review of an iron dextran product, FDA stated that, "aside from molecular weight differences (see discussion below) there may be other physicochemical differences resulting from probable different methods of production…which might matter in terms of efficacy."[9] In noting this, FDA acknowledges that a difference in the manufacturing process of these far less complicated iron dextran compounds could have a deleterious effect on the final product and its effectiveness. Based on Ferrlecit's large molecular weight and molecular complexity, one would expect it to be more susceptible to any change in the manufacturing process.

c. Physicochemical differences resulting from different methods of production could have a negative impact on the safety of a generic product.

Due to the complex nature of the manufacturing process, all attempts have been made to keep the procedures, equipment, and parameters the same over the last 40 years of production to assure a consistent final product. However, there have been several instances where certain parameters of the process were intentionally changed and resulted in an apparent increase in the reported adverse events.

In the mid 1990s, a marked increase in the number of adverse events reports was noted in data coming from Italy and Germany for Ferlixit® (the European brand name for Ferrlecit®). In the first half of 1995, a total of two adverse events were reported in Italy and four in Germany. In the second half of the same year, the adverse event incidence rose to 60 in Italy and 38 in Germany. After an exhaustive investigation of the manufacturing process, it was determined that the source of one of the ingredients of the product had been changed. Although both ingredients from both sources met the rigorous European Pharmacopoeia standards, substituting one for the other resulted in a dramatic change in the safety profile of the final product.[10]

In another case, a preservative-free version of Ferrlecit® was manufactured for use in a clinical study. The product was made in exactly the same manner as the commercial product except that preservative was eliminated. The preservative-free clinical trial material was manufactured using production equipment and production batch records according to the process used for the commercial production of the preserved Ferrlecit®. When used in the clinical study an unusually high number of patients discontinued from the study due to adverse events. Although the events cannot be definitely attributed to the change in Ferrlecit® formulation, it is reasonable to suspect that it was a contributing factor.

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[9] November 17, 1992 Amendment in Support of Pharmaceutical Equivalence and Waiver Request, ANDA#40-024, Iron Dextran Injection, USP, Luitpold Pharmaceuticals, Inc.

[10] Data on file at Watson Pharma.

4. Until the drug product is fully characterized, it is not possible to determine if a generic product is the "same" as Ferrlecit® as required under the FD&C act.

Since its development in 1959, there have been ongoing efforts to fully characterize the Ferrlecit® macromolecule. Much of the early work was performed by Dr. Keppler in Vienna and Heidelberg, Germany. Later research was performed by R&D Labs and Watson Laboratories to support the Ferrlecit® NDA.

Unfortunately, the molecular complexity of Ferrlecit® is high and no unambiguous structure can yet be assigned. Standard characterization techniques, such as nuclear magnetic resonance (NMR), have proved only partially effective for determining the structure of the Ferrlecit® macromolecule due to the paramagnetic ferric centers. X-ray crystallography is ineffective because of the amorphous nature of Ferrlecit® in fluid solution. However, some aspects of the structure may be inferred from other spectroscopic data and chemical analyses.

In 1997, extensive additional physiochemical testing using state-of-the-art testing was performed on Ferrlecit®[11] Based on these results, it was concluded that Ferrlecit® is an aqueous pH 8.5 solution containing an anionic high molecular weight polynuclear ferric species, benzyl alcohol and excess sucrose. There is no experimental evidence for the presence of Fe(II) sodium chloride or carbonate, or dextran.[12]

The structure proposed in 1997 consisted of a di-iron repeat unit bridged by carboxylate groups and hydroxo/oxo groups. The iron coordination number was determined to be six and the iron atoms in a high spin, S=6. If one assumes the average molecular weight of 350,000 (based on the best available data at the time), then the number of repeats of this unit shown in the figure would be about 200. To be consistent with the known reaction stoichiometry of Ferrlecit® [$Fe_2O_3(C_6H_{11}O_7)(C_{12}H_{22}O_{11})_5$], it was assumed that four sucrose molecules were directly coordinated with iron and that the additional sucrose molecule must be associated with the complex, presumably through hydrogen bonding to the other ligands.

More recent research sponsored by Watson Laboratories provides somewhat contradictory results. Recent analyses examined the physicochemical properties of a highly purified Ferrlecit® macromolecules which was then isolated as a lyophilized solid. It is important to note that the purification/lyophilization processes do not change the structure of the macromolecule as evidenced by the fact that the purified macromolecule has the same electronic structure as the macromolecule in the commercial product.

Using the purified product, experimental results provide no evidence for sucrose coordination to iron in lyophilized Ferrlecit. Elemental analysis of purified Ferrlecit®

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[11] Data on file at Watson Pharma.

[12] Data on file at Watson Pharma.

indicates the presence of one sodium atom per 14 iron atoms, compared to the previous results that indicated a ratio of 1:2. The ultrafiltration process removes 100% of the sucrose and 61% of the sodium gluconate. The present conclusions, based on all the evidence generated to date, is that the Ferrlecit® macromolecule is not associated with a significant quantity of sucrose and contains less sodium gluconate than previously believed. In addition, based upon the new data obtained for the purified Ferrlecit® macromolecule, the molecular weight ranges from approximately 340,000 to 750,000 daltons, higher than previously thought.

These results indicate that Ferrlecit® is an unusually complex macromolecule that is difficult to characterize, even with current state-of-the-art testing. Because of the paramagnetic nature of the ferric centers, the standard tests used for structural characterization are impossible to perform. As we employ each new method of characterization, we are finding out more about the nature of this complex macromolecule. However, because it is so difficult to accurately characterize the actual structure of the Ferrlecit® macromolecule, it will be impossible to demonstrate any sort of chemical comparability with a generic product without using the extensive test procedures that we have employed. Even performing this exhaustive barrage of tests may not guarantee that a generic product is structurally comparable to Ferrlecit® because one can only infer the structure from the results.

5. If the molecular weight of a generic product differs significantly from the molecular weight of Ferrlecit®, clinical studies should be required to demonstrate equivalent safety and effectiveness

FDA has previously raised concerns about the comparability of iron dextran products with different molecular weights. In 1991, Luitpold Pharmaceuticals filed an ANDA for its iron dextran product Dexferrum®. This application requested a waiver from using Imferon® as the reference listed drug because the manufacturer had removed that product from the market due to other problems. FDA denied Luitpold's request for a waiver based in part on the "dramatic difference in molecular weight between the test and reference drugs."[13] At FDA's request Luitpold tested the molecular weights of its product Dexferrum®, the former reference listed drug Imferon and the current RLD INFeD®. The FDA reviewer states that the molecular weight of Dexferrum® "differs immensely" from the values for Imferon and INFeD®[14] and the product labels indicate that Dexferrum is twice the molecular weight of INFeD.

Because of this dramatic difference in molecular weights, the FDA required Luitpold to perform additional clinical studies to demonstrate that the products were

[13] Review of Pharmacokinetic and Iron Utilization Studies, November 28, 1995, ANDA 40-024, Iron Dextran Injections, USP, supra at 2.

[14] Letter from FDA to Luitpold Pharmaceuticals, Inc., April 9, 1993, regarding Iron Dextran Injection, ANDA 40-024.

equivalent. The FDA required that a pharmacokinetics study and an iron utilization study (consisting of determining the degree of mobilization of iron from the iron dextran to ferritin storage and hemoglobin synthesis) be performed. Based on these results the FDA found that Dexferrum was therapeutically equivalent to INFeD®.

Although the products were shown to be comparable with respect to their effectiveness based on pharmacokinetics and iron utilization, there was no attempt to prove them comparable with respect to safety. It is possible that differences in their molecular weights could have an on effect on their respective safety profiles. In a retrospective study published in 2001, the authors analyzed the data from 841,252 administrations of intravenous iron dextran. Of this number there were 165 reported suspected adverse drug experiences. However, when the incidence of adverse events was compared by specific iron products, there were eight times more events in patients receiving Dexferrum® than in patients receiving INFeD®.[15]

These data may indicate that, although these products appeared equivalent based on measures of therapeutic equivalence (pharmacokinetics and iron utilization), they may, nevertheless, exhibit markedly different safety profiles. This illustrates the point that iron complexes are unique compounds that may not behave in the body as do conventional drugs. Because two iron compounds have been shown to be therapeutically equivalent does not assure that they will have the same safety profile, especially when they are physicochemically different.

If products differ significantly in molecular weight or other physicochemical parameters, clinical studies should be required to demonstrate equivalent safety. As a condition of approval, the FDA required that Watson Pharma perform a large, multicenter, placebo-controlled clinical study to evaluate the safety of Ferrlecit®.[16] This study involved almost 2,600 patients and should serve as the model for comparing the safety of parenteral iron products.

6. The FDA considers parenteral colloidal solutions to be a problem and requires additional testing to confirm equivalence.

As stated by the FDA in its review of Dexferrum®, "[a]nother problem is that iron dextran is not a true solution....As with parenteral suspensions, parenteral colloidal

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[15] Fletes R, Lazarus JM, Gage J, Chertow GM. Suspected iron dextran-related adverse drug events in hemodialysis patients. Am J Kidney Dis. 2001 Apr;37(4):742-9

[16] Michael B, Coyne, DW, Fishbane S, et. al. Sodium ferric gluconate complex in hemodialysis patients: adverse reactions compared to placebo and iron dextran. Kidney Int. 2002 May;61(5):1830-9.

solutions are considered by the Division of Bioequivalence to be a problem and waivers of in vivo bioequivalence studies are not granted on them."[17]

Like iron dextran, Ferrlecit® is a colloidal solution, i.e., a heterogeneous mixture of ferric gluconate particles in an aqueous sucrose solution, and as a result presents the same barrier for granting a waiver of in vivo bioequivalence study requirements. Add to this problem the issues already discussed, including Ferrlecit's complex structure, manufacturing process, difficulty in characterization, molecular weight, and it becomes clear that producing a generic product with the same physicochemical properties and the same safety and effectiveness profiles will be challenging if not impossible. In fact, many of these issues would directly impact on a generic applicant's ability to demonstrate or claim that its product was the "same" as the reference listed drug, Ferrlecit®.

C. Conclusions

Based on the above information, for a generic manufacturer to produce sodium ferric gluconate complex in sucrose for injection that is the "same" as Ferrlecit® under the Statute, the applicant must demonstrate that.

1. The process used to manufacture the generic product has been adequately shown to be the same as Watson's manufacturing process for Ferrlecit®, and

2. The physiocochemical characteristics of the generic product are the same as those of Ferrlecit®, and

3. The active ingredient, or in this case, the final product of the generic version is the "same as" that of Ferrlecit®.

If all of the above requirement cannot be met then the FDA should require an NDA supported by a demonstration of equivalent safety and effectiveness based on results of appropriate preclinical and clinical studies.

[17] See Review of Pharmacokinetic and Iron Utilization Studies, March 21, 1995, supra at 2.

D. Environmental Impact

The actions requested herein are subject to categorical exclusion under 21 CFR §§ 25.30 and 25.31(a).

E. Economic Impact

An economic impact statement will be submitted if requested by the Commissioner.

F. Certification

The undersigned certifies that, to the best knowledge and belief of the undersigned, this petition includes all information and views on which the petition relies, and that it includes representative data and information known to the petitioner that are unfavorable to the petition.

Mary E. Norvitch 3/13/04

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Respectfully submitted,

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Attachments